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# THE CHRONIC EFFECTS OF JP-8 JET FUEL EXPOSURE ON THE LUNGS



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## SUMMARY ABSTRACT

This research has resulted in four separate projects. The first project was the exposure of Fischer 344 male rats to JP-8 jet fuel, mean concentration of  $497 \pm 32.1 \text{ mg/m}^3/\text{hr}$ , for 7 or 28 days. This exposure resulted in changes in pulmonary function and lung chemical mediators, specifically Substance P, after 28 days of exposure. The second project dealt with blocking the increase in Substance P in these rats by a pre-treatment regimen with capsaicin before jet fuel exposure. Capsaicin caused a further increase in lung permeability and a million-fold increase in airway sensitivity to histamine after the 7-day jet fuel exposure. The third project dealt with the effects of a 7-day jet fuel exposure in congenic mice who were deficient in the inducibility of the aryl hydrocarbon hydroxylase enzyme. These mice are relatively resistant to the effects of jet fuel-induced lung injury. The fourth project investigated the effects of the jet fuel exposure on secondary organs, specifically the liver, spleen, and kidneys. There were pathological differences in the liver, spleen, and kidneys between the 7-day jet fuel exposure group and baseline controls. However, some of these differences were not apparent in the 28-day exposure group, possibly indicating compensatory mechanisms to the exposure.

## STATEMENT OF WORK

There will be a total of 372 rats utilized in the study. The rats will be divided into the following groups-

- (1) Baseline Control, (N=12). These rats will be killed at the start of the study to establish baseline values on all the parameters to be examined in the study.
- (2) Longitudinal Control, (N=180). These rats will undergo exposure to sham air.
- (3) JP-8 Jet Fuel-Exposed, (N=180). These rats will be exposed to either of the three concentrations of JP-8 jet fuel ( $30 \text{ mg/m}^3$ ,  $300 \text{ mg/m}^3$ , or  $1020 \text{ mg/m}^3$ ) for one of the four exposure time periods (1 day, 7 days, 28 days, or 56 days).

The parameters we will study are the following-

- (1)  $^{99m}\text{TcDTPA}$  pulmonary epithelial permeability of each rat.
- (2) Lung mechanics of dynamic and static lung compliance, work of breathing, power of breathing, respiratory time constant, and lung resistance on each rat.
- (3) Measure lung eicosanoids, TNF, IL-1, and Substance P in nine rats in each group.
- (4) Pathologic studies of wet lung weight/body weight ratio, electron and light microscopy in three rats in each group.
- (5) Alveolar macrophage studies in nine rats in each group.
- (6) Pharmacological blocker studies of Substance P, N=6 for each JP-8 jet fuel exposure group and their corresponding longitudinal control group, N=6.

The proposed study will take three years to complete. We believe it is essential to standardize our study timetable as much as possible to minimize the effects of variables such as seasonal variations of temperature, humidity, and pollen count on our rat population. Consequently, we propose to complete 124 rats/year for the three years of the study with equal numbers of rats from each group completed in each of the yearly time sequences.

## FIRST PROJECT

The first project was the exposure of Fischer 344 male rats to JP-8 jet fuel, mean concentration of  $497 \pm 32.1 \text{ mg/m}^3/\text{hr}$ , for 7 or 28 days. This exposure resulted in changes in pulmonary function and lung chemical mediators, specifically Substance P, after 28 days of exposure. The following groups were given JP-8 jet fuel exposure for 1 hour/day: 7D (N=14)- seven days of exposure, 28D (N=11)- twenty-eight days of exposure, and BC (N=7)- no exposure. The rats were anesthetized and pulmonary epithelial permeability was measured by clearance of technetium-labeled diethylenetriamine pentaacetate ( $^{99m}\text{TcDTPA}$ ) k (% clearance/min). The  $^{99m}\text{TcDTPA}$  k values were significantly ( $p < 0.05$ ) increased in both 7D ( $2.2 \pm 0.2$ ) and 28D ( $2.5 \pm 0.4$ ) compared to BC ( $1.2 \pm 0.2$ ), the 7D longitudinal control group ( $1.1 \pm 0.1$ ), and the 28D longitudinal control group ( $0.9 \pm 0.3$ ). The rats were killed, heart-lung block removed, and broncho-

alveolar lavage (BAL) performed with normal sterile saline. BAL Substance P levels were significantly increased in the 28D group ( $13.6 \pm 1.8$  fmol/ml BAL fluid) compared to BC ( $4.9 \pm 1.2$  fmol/ml BAL fluid). Conversely, 6-keto-PGF<sub>1</sub>alpha (stable metabolite of prostacyclin, PGI<sub>2</sub>) BAL concentrations were decreased in 28D,  $538.6 \pm 25.6$  pg/ml -vs-  $642.7 \pm 13.5$  pg/ml for BC. There were no differences in BAL thromboxane, leukotriene B<sub>4</sub>, and leukotriene C<sub>4</sub> between any groups. An analysis of BAL total white cell count showed that both the 7D and 28D groups had increases in total white cell count compared to the other groups, however, the differences were not significant. In addition, the BAL cell differentials were not different between any groups, with the predominant cell in the lung being alveolar macrophages. The 28D group had a significant increase in inspiratory resistance (cm H<sub>2</sub>O/L/sec) of  $1775 \pm 733$  -vs-  $1203 \pm 600$  for the 28D longitudinal control group. Superoxide production was measured in cultured alveolar macrophages from the BC, 7D, and 28D groups and there was no difference between groups in their ability to produce superoxide after stimulation with phorbol myristate acetate. Pathological studies of the 7D and 28D rats showed no significant lung injury as shown by light microscopy. We intend to conduct electron microscopy studies in Year 2 of the project.

#### Conclusions:

- (1) Chronic JP-8 jet fuel exposure at a moderate concentration causes lung injury as evidenced by increases in alveolar epithelial permeability, changes in chemical mediator concentration, and increased pulmonary resistance.
- (2) The increase in <sup>99m</sup>TcDTPA alveolar epithelial permeability was present at 7 days after exposure to JP-8 jet fuel and the additional exposure in the 28D group did not increase alveolar epithelial permeability appreciably.
- (3) Chronic JP-8 jet fuel exposure does not appear to alter alveolar macrophages' ability to produce the superoxide radical.
- (4) Light microscopy does not show any evidence of lung injury in 7D or 28D groups.

### Speculation:

We speculate that the increase in alveolar epithelial permeability may occur as early as 7 days after exposure to JP-8 jet fuel and may allow more aeroallergens as well as jet fuel to gain access to the lung parenchyma. This phenomenon causes the initiation of an inflammatory process in the lungs. Substance P levels in the lungs increase due to the inflammatory process initiated by increased alveolar epithelial permeability. Substance P can induce constriction in bronchial smooth muscle and may be responsible for the increase in inspiratory resistance observed in the 28D group.

### SECOND PROJECT

We decided to investigate the role of Substance P further in our rat model of JP-8 jet fuel exposure based on the findings of Project 1. We pre-treated rats with capsaicin, a Substance P blocker, at a dose of 25 mg/kg body weight for six days before exposure to JP-8 jet fuel for seven days at the same concentration as in Project 1. The capsaicin pre-treated JP-8 jet fuel exposed rats (N=8) had a mean  $^{99m}\text{TcDTPA}$  k value of  $2.77 \pm 0.33$  which was significantly higher than the saline pre-treated JP-8 jet fuel exposed rats (N=11) mean  $^{99m}\text{TcDTPA}$  k value of  $1.93 \pm 0.22$ . There were no significant differences in the BAL Substance P values between the two groups. However, the broncho-alveolar lavage was conducted after administration of two boluses of histamine, 10 mg/ml and 50 mg/ml, into the lungs to test for airway hyperreactivity. The saline pre-treated JP-8 jet fuel exposed rats had a significant increase in their inspiratory resistance (cm H<sub>2</sub>O/L/sec) after 50 mg/ml histamine compared to their baseline value,  $1692 \pm 85$  -vs-  $1435 \pm 45$ . However, the capsaicin pre-treated JP-8 jet fuel exposed rats had a significant increase in inspiratory resistance after only 10 mg/ml histamine,  $1492 \pm 35$  -vs-  $1342 \pm 77$ . The provocative dose of histamine that will increase inspiratory resistance 150% (PC 150) is dramatically different between the two groups. The PC 150 for the capsaicin pre-treated JP-8 jet fuel exposed rats was 57 mg/ml histamine while the saline pre-treated JP-8 jet fuel exposed rats had a million-fold difference of a PC150 > 1,000,000 mg/ml histamine. These differences in PC 150 do not exist in the capsaicin pre-treated sham JP-8 jet fuel exposed or saline pre-treated sham JP-8 jet fuel exposed groups. It is well known that histamine can cause the

release of Substance P from C-nerve fibers. Thus, we will conduct experiments with no histamine challenge to observe the differences in BAL Substance P values between the two groups. There were no differences in BAL total white cell counts or cell differentials.

#### Conclusions:

- (1) Capsaicin pre-treatment before JP-8 jet fuel exposure causes a significant increase in alveolar epithelial permeability compared to saline pre-treatment before JP-8 jet fuel exposure.
- (2) Capsaicin pre-treatment before JP-8 jet fuel exposure causes an increased sensitivity to histamine as demonstrated by the million-fold difference in the PC150 for the capsaicin pre-treated rats compared to the saline pre-treated group.

#### Speculation:

We speculate that capsaicin pre-treatment modifies the alveolar epithelial intracellular tight junctions, possibly by altering electrostatic charge, and this mechanism causes the increase in alveolar epithelial permeability. This same phenomenon may be acting at the airway epithelial cell intracellular tight junctions to increase airway epithelial permeability. Thus, aeroallergens and JP-8 jet fuel have a greater access to the lung interstitium and an inflammatory response is initiated. On the other hand, the increase in airway epithelial permeability may allow more histamine to gain access to airway smooth muscle and cause constriction. This phenomenon may explain the dramatic difference in PC150 between the two groups.

### THIRD PROJECT

We have worked with Dr. Robert Erickson, a well-known genetics expert in the Department of Pediatrics, who has developed a congenic mouse model that is deficient in its inducibility to produce the aryl hydrocarbon hydroxylase (AHH) enzyme. This enzyme plays a role in metabolizing hydrocarbon compounds and is also found in humans. The congenic mice have a similar, 99.99%, genomic structure. They are produced through genetic manipulation of twenty successive generations in which every other generation is the product of a brother-sister breeding. It is estimated that the cost of

developing a congenic mouse strain is approximately \$2,000/mouse. The U.S. Air Force was not billed for the cost of the mice in Project 3.

The influence of AHH activity on lung injury from a seven day exposure to JP-8 jet fuel was tested in a control (C57BL6 mice) or variant mice (AHH-deficient,  $Ah^d$ ) (Table 1). Lung function was determined during mechanical ventilation by the PEDS-LAB® computerized pulmonary function measurement system. There was a significant difference ( $p = 0.03$ ) in pulmonary resistance between the two groups [ $13,366 \pm 659$  for the C57BL6 JP-8 mice compared to  $9,852 \pm 1,409$  cm/H<sub>2</sub>O/L/sec] for the  $Ah^d$  mice after JP-8 exposure.

Table 1

<u>Group</u>	<u><math>^{99m}TcDTPA</math> k</u>
C57BL6 JP-8 Exposed (N=6)	3.9 (0.4)
$Ah^d$ JP-8 Exposed (N=19)	3.3 (0.4)
C57BL6 Controls (N=8)	3.0 (0.6)
$Ah^d$ Controls (N=10)	4.2 (0.5)

$^{99m}TcDTPA$  k values are mean ( $\pm$  SEM). There are significant differences between the JP-8 jet fuel exposed groups and their controls. Based on Project 1, one would expect that the 7 day JP-8 jet fuel exposure would cause an increase in  $^{99m}TcDTPA$  k and the C57BL6 mice follow this pattern. However, the  $Ah^d$  mice exposed to JP-8 jet fuel had a lower alveolar epithelial permeability than their sham controls. This finding demonstrates that the  $Ah^d$  mice exposed to JP-8 jet fuel did not have the expected increase in alveolar epithelial permeability that is evidence of lung injury.

#### Conclusions:

- (1) The aryl hydrocarbon hydroxylase enzyme is involved in the metabolism of JP-8 jet fuel because the mice deficient in the inducibility of the AHH enzyme had less lung injury than their controls as demonstrated by a decreased alveolar epithelial permeability.



### Speculation:

We speculate that the AHH-deficient mice metabolize the JP-8 jet fuel at other organ sites, specifically the liver and/or kidneys, other than the lung. Thus, even though there is less lung injury in the AHH-deficient mice, there may be more tissue injury at other sites other than the lungs. We are presently testing this hypothesis by conducting pathology and enzyme tests on liver tissue from AHH-deficient mice.

### FOURTH PROJECT

This project dealt with the effects of JP-8 jet fuel exposure at other organ sites other than the lungs. The organ sites investigated were the liver, kidneys, and spleen. Fischer 344 male rats were assigned to five groups which were; baseline control (N=18), longitudinal control for 7 days (N=14), longitudinal control for 28 days (N=16), 7D JP-8 jet fuel exposed (N=22), and 28D JP-8 jet fuel exposed (N=17). Assay performed for serum ALT, AST, and BUN were within normal levels for the age and gender of the rats. Significant differences occurred between the JP-8 treated groups and controls, but more data is required to determine if this difference has any physiological relevance. Specifically, BUN in 28D JP-8 jet fuel exposed rats was significantly lower ( $p < 0.05$ ) than the 28D longitudinal control group.

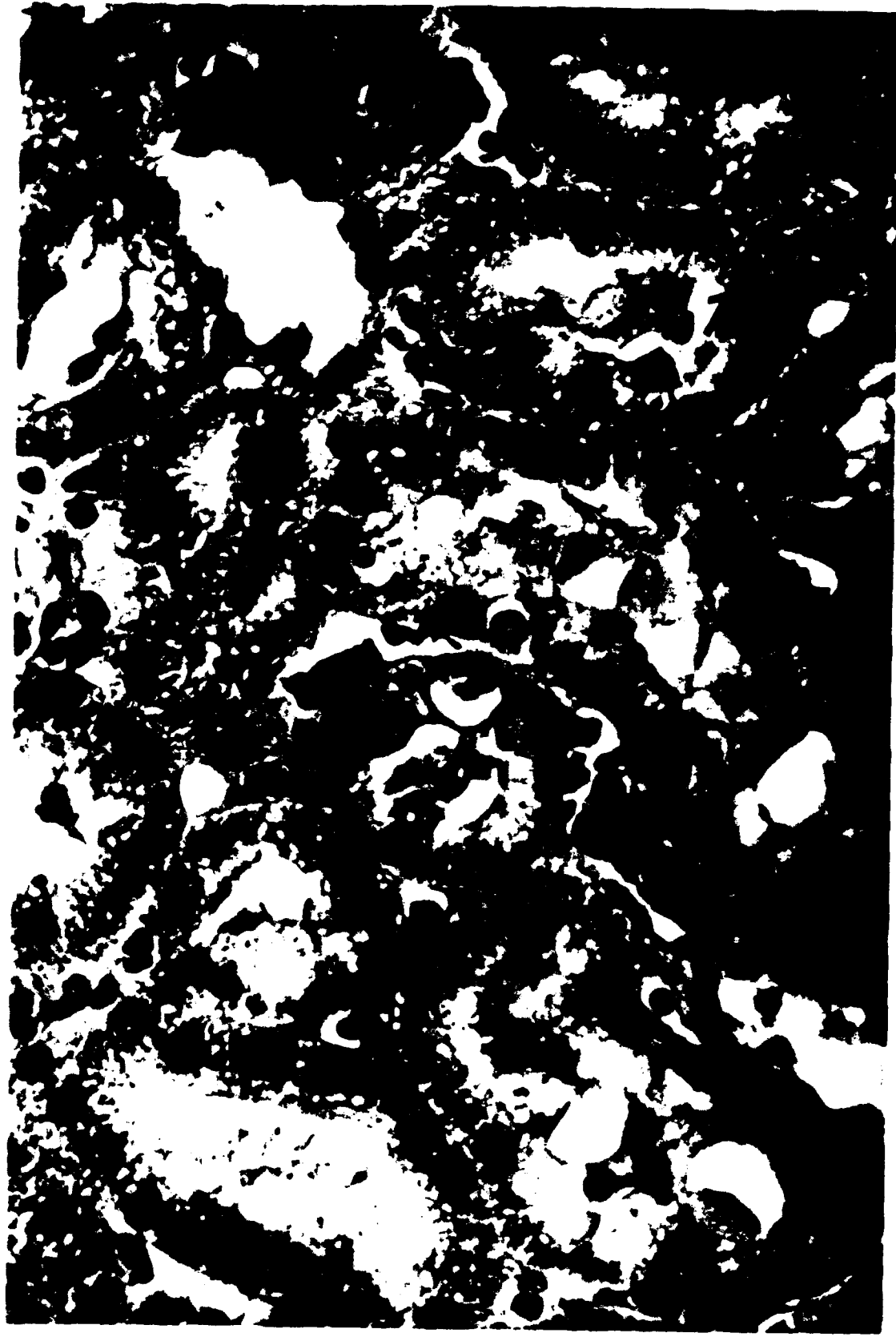
The pathological studies of the kidneys from the 28D JP-8 jet fuel exposed rats demonstrated the kidneys have a greater amount of protein droplets consistent with alpha-2-microglobulin protein nephropathy (Figures 1 and 2). The significance of male rat-specific protein nephropathy, possibly involving the alpha-2-microglobulin enzyme, has not yet been fully investigated in our study. Mallory's Heidenhain stain was used with a small sample to measure the quantity of the droplets. The 28D JP-8 jet fuel exposed group have higher droplet scores; however, a larger sample must be evaluated.

The liver did not demonstrate any pathological changes, but liver microsome androstenedione assays indicate that inhibition has occurred when measuring 16 alpha metabolites. These differences were highly significant between the BC and 7D and 28D JP-8 jet fuel exposed groups.

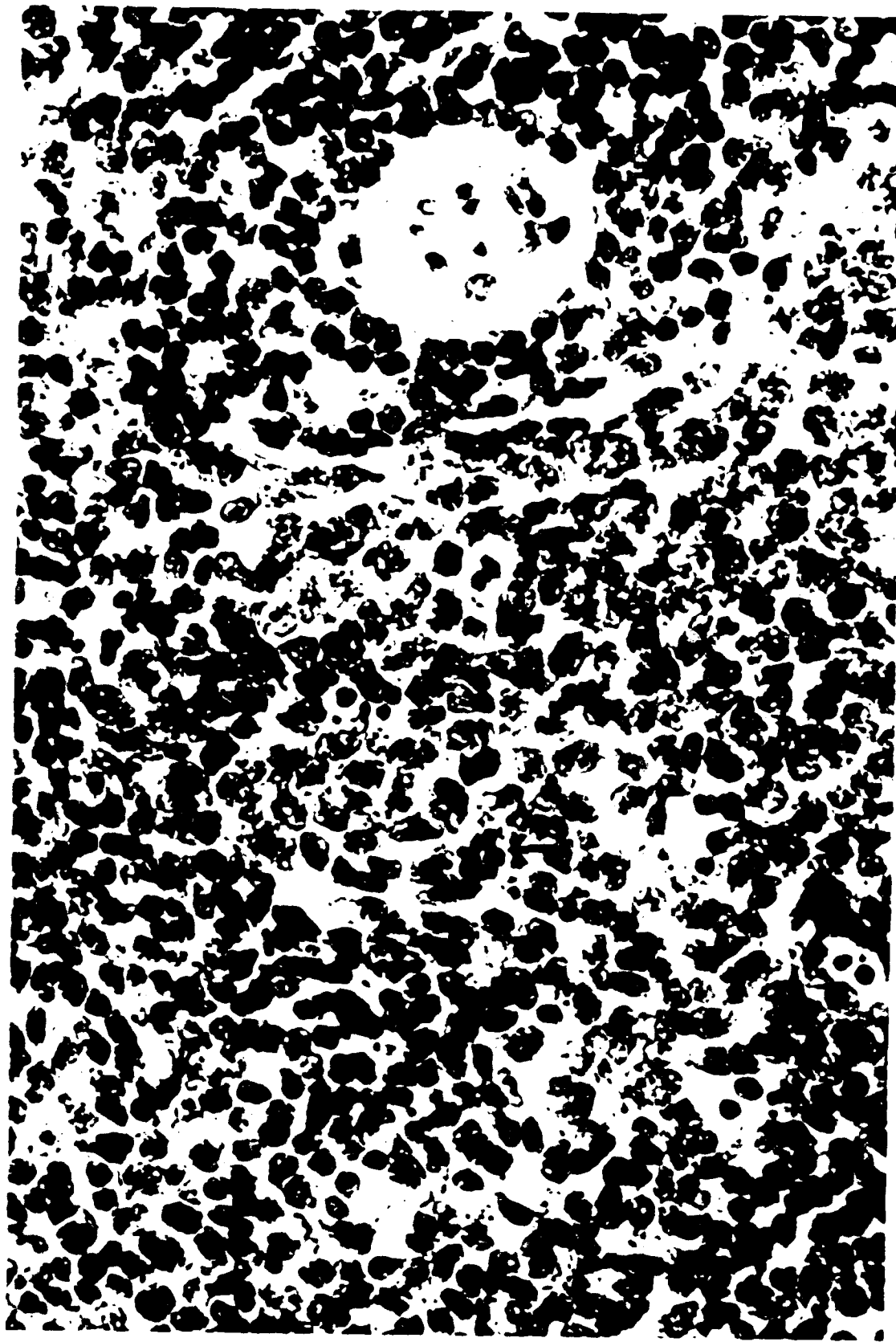
Histologic studies of the spleen demonstrate significantly more JP-8 jet fuel induced injury in the lymphoid follicles in the 28D JP-8 jet fuel exposed group (Figure 3). The spleen weight/body weight



**Figure 1.** Light microscopy of the kidney of a JP-8 jet fuel-exposed (7 days) male Fischer 344 rat. There is increased fluid accumulation in the kidney lumen. Arrows indicate protein droplets possibly associated with alpha-2-microglobulin.



**Figure 2.** Light microscopy of the kidney of a JP-8 jet fuel-exposed (28 days) male Fischer 344 rat. There are increased protein droplets compared to 7 day exposure rats (arrows).



**Figure 3.** Light microscopy of the spleen of a JP-8 jet fuel-exposed (28 days) male Fischer 344 rat. Arrows indicate degenerating lymphocytes.

ratio was higher in the 7D JP-8 jet fuel exposed group compared to the 28D JP-8 jet fuel exposed group. This finding was also present in the kidney weight/body weight ratio. These significant differences in kidney and spleen weight ratios at 7 days but not at 28 days may indicate that compensatory mechanisms may be activated after a minimal exposure to JP-8 jet fuel. Brain tissue has been saved for pathological studies, but they have not been studied at this point in time.

#### Conclusions:

- (1) Chronic lung exposure to JP-8 jet fuel, as little as 7 days, can cause secondary organ injury to the liver, kidneys, and spleen.
- (2) There seems to be a compensatory mechanism(s) that is activated after as few as 7 days of JP-8 jet fuel exposure in the kidney and spleen.

#### Speculation:

We do not know the chemical nature of the JP-8 jet fuel after it has been metabolized at the primary organ of exposure, the lungs. Thus, it would be very important to learn how the lungs metabolize JP-8 jet fuel before it passes through the systemic circulation to the secondary organ sites of the liver, kidneys, and spleen to induce injury. This is one of the goals of the congenic mouse study since we eliminate genetic variability in the lungs. Thus, if we can determine the JP-8 jet fuel metabolism processes that occur in the congenic mouse's lungs before the metabolized jet fuel moves into the systemic circulation, we can begin to understand how secondary organ sites are injured.

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- (2) Witten ML, Pfaff JK, Parton K, Lantz RC, Carter D, Leeman SE: JP-8 jet fuel exposure alters lung chemical mediator and substance P activity in rats. THE FASEB JOURNAL, 1992, 6:A1065.
- (3) Chen H, Witten ML, Pfaff JK, Lantz RC, Carter D: JP-8 jet fuel exposure increases alveolar epithelial permeability in rats. THE FASEB JOURNAL, 1992, 6:A1064.
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- (6) Pfaff J, Parton K, Lantz R, Chen H, Carter D, Witten M: Effects of JP-8 jet fuel exposure on pulmonary function. AMERICAN REVIEW OF RESPIRATORY DISEASE, 1992, 145:A89.
- (7) Witten ML, Figueroa JT, McKee JL, Lantz RC, Quan SF, Sobonya RE, Lemen RJ: Fractal and morphometric analysis of lung structures after canine adenovirus-induced bronchiolitis in beagle puppies. PEDIATRIC PULMONOLOGY (submitted).
- (8) Pfaff JK, Parton K, Lantz RC, Figueroa JT, Chen H, Hall J, Witten ML: Chronic exposure to JP-8 jet fuel causes lung injury in rats. EXPERIMENTAL LUNG RESEARCH (in preparation).

- (9) Witten ML, Pfaff JK, Parton K, Lantz RC, Chen H: The role of Substance P in regulating alveolar permeability after exposure to JP-8 jet fuel. JOURNAL OF APPLIED PHYSIOLOGY (in preparation).
- (10) Witten ML, Pfaff JK, Parton KH, Lantz RC, Hays A, Chen H, Leeman SE: Capsaicin pre-treatment before JP-8 jet fuel exposure causes a large increase in airway sensitivity in rats. (in preparation for submission to the International Substance P Conference in Shizuoka, Japan on November 3-6, 1992).

### **PARTICIPATING PROFESSIONALS**

- (1) Mark L. Witten, Ph.D. Principal Investigator  
University of Arizona College of Medicine
- (2) Susan E. Leeman, Ph.D. Consultant  
Boston University College of Medicine
- (3) Robert C. Lantz, Ph.D. Co-Investigator  
University of Arizona College of Medicine
- (4) Dean E. Carter, Ph.D. Consultant  
University of Arizona College of Pharmacy
- (5) John K. Pfaff, M.D. Fellow  
Lt. Commander, U.S. Navy Medical Corps
- (6) Kathy H. Parton, D.V.M. Master's Student  
University of Arizona College of Pharmacy
- (7) Huizhong Chen, M.D. Visiting Scientist  
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University of Arizona College of Medicine

- |      |  |                     |
|------|--|---------------------|
| (11) | Jason T. Figueroa                            | High School Student |
|      | University High School                       |                     |
| (12) | Roni Grad, M.D.                              | Consultant          |
|      | University of New Mexico College of Medicine |                     |
| (13) | Robert P. Erickson, M.D.                     | Consultant          |
|      | University of Arizona College of Medicine    |                     |

**Advance Degrees Awarded:**

- (1) Dr. Parton is currently pursuing a Master's degree in the Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona. She has just started work on her Master's Thesis which is based on Project 4 of our research project.

**COUPLING ACTIVITIES**

There have been no coupling activities. We have been visited by Captain Donald R. Tocco, a research toxicologist, from the Armstrong Aerospace Medical Research Laboratory at Wright-Patterson Air Force Base. Dr. Tocco was visiting the Department of Pharmacology and Toxicology and we arranged for him to visit our laboratory while we were performing experiments on the Air Force project.

**DISCOVERIES, INVENTIONS, PATENT DISCLOSURES, AND SPECIFIC APPLICATIONS**

There have been no discoveries, inventions, patent disclosures and specific applications generated from the Air Force project at this point in time.



## RESEARCH ACCOMPLISHMENTS AND PLANS FOR YEAR TWO OF THE CURRENT PROJECT-

We believe that we have accomplished a large amount of the research that was in the STATEMENT OF WORK when the grant proposal was submitted to the Air Force Office of Scientific Research. Furthermore, all of this work has been accomplished in approximately the last 10 months because of the start-up time of two months while equipment was ordered, delivered, and made operational.

We have generated two additional research projects, Projects 3 and 4, that will add substantial new information to our study of the chronic effects of JP-8 jet fuel exposure in the areas of genetics and secondary organ injury. These projects have been initiated at very little cost to the Air Force. For example, we estimate that we have used approximately \$75,000 in congenic mice at the cost of \$150/month per diem for housing and maintenance to the Air Force.

Our plans for Year 2 of the project include following the general outline of the STATEMENT OF WORK. We will conduct studies at the maximum time interval of 56 days and at the maximum concentration of JP-8 jet fuel of 1,000 mg/m<sup>3</sup>/hour. In addition, we have purchased a new exposure chamber from excess funds in the Personnel section of the first year grant budget. This new exposure chamber allows for heat dissipation by a special design. Thus, we now have the capability to conduct longer (> 1 hour) exposures with the JP-8 jet fuel without the danger of heat stress to the rats. During our visits with Air Force personnel at Davis-Monthan Air Force Base in Tucson, Arizona; we were informed that the fueling crews typically spent more than two hours in an eight-hour shift actually refueling aircraft. Thus, we now have the capability to match our rat exposure more closely with the actual exposure that Air Force personnel undergo in the performance of their duties. We will also continue our work in Projects 3 and 4 which examine the genetics and secondary organ injury after chronic exposure to JP-8 jet fuel.